IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#18

In re: U.S. Patent No. 4,755,534

Issued: July 5, 1988

To: Anton Steutz

For: HYDROPENYLAMINES, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND THEIR USE AS PHARMACEUTICALS

Honorable Commissioner
of Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

Attached in duplicate is an Application for Patent Extension under 35 USC 156 for the above-identified United States patent.

The Commissioner is hereby authorized to charge the $1000 fee under 37 CFR 1.20(j) and any additional fee due in connection with the filing of this Application for Patent Extension to Deposit Account No. 19-0134 in the name of Sandoz Corporation.

This paper is submitted in triplicate along with a return postcard.

Respectfully submitted,

Carl W. Battle
Registration No. 30,731
(201) 503-8177

CWB:lmc

SANDOZ CORPORATION
59 Route 10
E. Hanover, N.J. 07936

DF11303 03/22/93 4755534 19-0134 110 111 1,000.00CH

February 25, 1993

Enclosures: Application for Patent Extension (in duplicate);
Return Postcard;
This page submitted in triplicate

Case No. 900-9253/CIP

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Express Mail Mailing Label Number TB216846080US

Date of Mailing February 25, 1993

I hereby certify that on the date indicated above this application for Patent Extension for USP 4,755,534

is being deposited with the United States Postal Service as Post Office to Addressee Express Mail addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231 in accordance with 37 CFR 1.10.

Antoinette Lombardi

Signature of Person Mailing the Application

Antoinette Lombardi

Printed or Typed Name of Person Mailing the Application

THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 4,755,534

Issued: July 5, 1988

To: Anton Steutz

For: PROPENYLAMINES, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND THEIR USE AS PHARMACEUTICALS

Honorable Commissioner
of Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

I. Applicant, Sandoz Ltd. (also known as SANDOZ AG), a corporation incorporated under the laws of Switzerland, with its registered office at Basle, Switzerland, represents that it is the owner of the entire right, title and interest in and to United States Letters Patent No. 4,755,534 identified above by virtue of assignments in favor of:

1. Sandoz Ltd. from and by Anton Steutz recorded at the U.S. Patent and Trademark Office on April 7, 1988 under Reel 4847 and Frame 783;

2. Fidelity Union Trust Company from and by Sandoz Ltd. recorded at the U.S. Patent and Trademark Office on December 21, 1990 under Reel 5550 and Frame 656; and

3. Sandoz Ltd. from and by First Fidelity Bank, National Association New Jersey, hereinafter referred to as "FIRST FIDELITY BANK, N.A." formerly First National State Bank, formerly Fidelity Union Bank/First National State, formerly Fidelity Union Bank, National Association, formerly Fidelity Union Bank, formerly Fidelity Union Trust Company, dated February 1, 1993 and submitted to the U.S. Patent and Trademark Office on February 4, 1993.

A copy of the Assignment to Sandoz Ltd. from the First Fidelity Bank, N.A. is attached hereto as Appendix A. The change in name of the Fidelity Union Trust Company to the First Fidelity Bank, N.A. is recorded as follows:

a) From the Fidelity Union Trust Company to the "Fidelity Union Bank" (Reel 4507 Frame 368).

b) From the Fidelity Union Bank, to the "Fidelity Union Bank, National Association" (Reel 4507 Frame 369).

c) From the Fidelity Union Bank, National Association, to the "Fidelity Union Bank/First National State" (Reel 4507 Frame 377).

d) From the Fidelity Union Bank/First National State to the "First National State Bank" (Reel 4507 Frame 378).

e) From the First National State Bank to the "First Fidelity Bank, National Association, New Jersey" (Reel 4507 Frame 379).

II. Applicant submits this Application for Extension of Patent Term under 35 USC 156 by providing the following information as required by 37 CFR 1.710 through 1.785, especially 1.740.

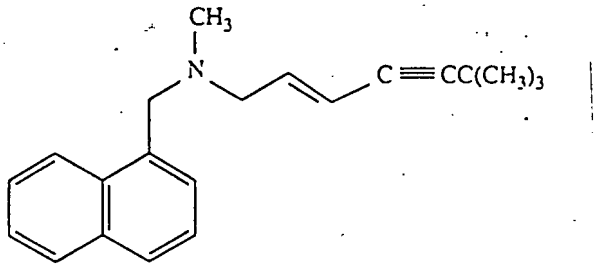
1. The complete identification of the approved product is:

chemical name: (1) trans-N-methyl-N-(1-naphthylmethyl)-6,6-dimethylhept-2-en-4-ynyl-1-amine hydrochloride, and

(2) (E)-N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalenemethanamine hydrochloride.

generic name: terbinafine hydrochloride

chemical structure:



2. Regulatory Review has taken place under the Federal Food, Drug and Cosmetic Act (21 U.S. Code 355) Section 505(b).

3. The product received permission for commercial marketing or use under the Federal Food, Drug and Cosmetic Act Section 505(b) on December 30, 1992.

4. The sole active ingredient in the approved product is terbinafine hydrochloride at a 1% level in a cream base for topical dermatologic use; and terbinafine hydrochloride, terbinafine base, or any other salt thereof has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act.

5. This application is being submitted within the sixty (60) day period permitted for submission pursuant to 37 CFR 1.720(f). The last day on which this application could be submitted is February 28, 1993.

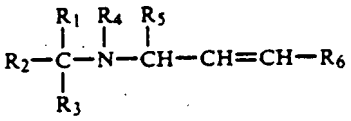
6. The U.S. patent for which an extension is being sought is U.S. patent 4,755,534, patented by Anton Steutz on July 5, 1988, and expiring normally on July 5, 2005.

7. A copy of U.S. patent No. 4,755,534 is attached hereto as Appendix B.

8. A copy of the Maintenance Fee Statement for U.S. patent 4,755,534 dated January 16, 1992 indicating that the first maintenance fee has been paid is attached hereto as Appendix C. No disclaimer, certificate of correction, or re-examination certificate has been issued or is of relevance in connection with U.S. patent 4,755,534.

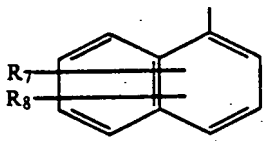
9. U.S. patent 4,755,534 claims the approved product terbinafine hydrochloride, a composition containing the product, or its use in claims 1, 4, 5, 6 and 7.

i) **1. A compound of the formula:**



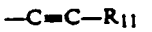
I

wherein the double bond is in the trans configuration and R_1 is a radical of formula IIa,



IIa

R_2, R_3, R_5, R_7 and R_8 are each hydrogen,
R_4 is methyl, and
R_6 is a radical of formula IIIa



IIIa

where R_{11} is n-butyl, tertiary butyl or phenyl or a chemotherapeutically acceptable acid addition salt thereof.

When R_{11} is tertiary butyl, claim 1 reads on terbinafine.

ii) **4. N-Methyl-N-(1-naphthylmethyl)-6,6-dimethyl-hept-2(trans)-en-4-ynyl-1-amine or a chemotherapeutically acceptable acid addition salt thereof.**

Claim 4 reads on terbinafine, and when the acid addition salt is hydrochloride, claim 4 reads on terbinafine hydrochloride.

iii) **5. A compound as claimed in claim 1 in the form of its hydrochloride.**

Claim 5 is dependent on claim 1 and reads on terbinafine hydrochloride.

iv) **6. A chemotherapeutical composition comprising an effective amount of a compound as claimed in claim 1 or a chemotherapeutically acceptable acid addition salt thereof in admixture with a chemotherapeutically acceptable diluent or carrier.**

Claim 6 is dependent on claim 1 and reads on a composition containing terbinafine or terbinafine hydrochloride.

v) **7. A method of treating diseases or infections caused by mycetes which comprises administering to a subject in need of treatment an effective amount of a compound as claimed in claim 1 or a chemotherapeutically acceptable acid addition salt thereof.**

Claim 7 is dependent on claim 1 and reads on a method of treating diseases or infections using terbinafine or terbinafine hydrochloride.

10. The relevant dates and information required pursuant to 35 USC 156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

a) The investigational new drug (IND) application for terbinafine hydrochloride was submitted by Pharmaquest/Sandoz LTD. (Vienna) to The Food and Drug Administration (FDA) on June 6, 1983. The effective date of the IND was June 6, 1983, and the IND number assigned was 22,218. IND 22,218 was transferred to Sandoz Pharmaceuticals Corporation (E. Hanover, N.J.), a wholly owned affiliate of Sandoz LTD., on December 22, 1992.

b) The date on which the new drug application (NDA) was submitted was June 30, 1991 and the NDA number assigned was 20-192; and

c) The date on which NDA 20-192 was approved was December 30, 1992.

11. Attached as Appendix D is a brief description of the significant activities undertaken by Pharmaquest/Sandoz LTD. and Sandoz Pharmaceuticals Corporation during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

12. In the opinion of Sandoz Ltd., U.S. Patent 4,755,534 is eligible for the extension herein applied for because it satisfies all of the requirements for such extension as follows:

(i) 35 USC 156(a)
U.S. patent 4,755,534 claims a product and a method of using a product.

(ii) 35 USC 156(a)(1)
The term of U.S. patent 4,755,534 has not expired before submission of this application.

(iii) 35 USC 156(a)(2)
The term of U.S. patent 4,755,534 has never been extended.

(iv) The application for extension is submitted by the owner of record.

(v) 35 USC 156(a)(4)
The product, terbinafine hydrochloride, has been subject to a regulatory review period before its commercial marketing or use.

(vi) 35 USC 156(a)(5)(A)
The commercial marketing or use of the product, terbinafine hydrochloride, after the regulatory review period indicated herein is the first permitted commercial marketing or use of the product under provisions of the Federal Food, Drug and Cosmetic Act (21 USC 355) under which such regulatory review occurred.

The length of the extension requested is 543 days, and was determined by the following calculation:

(A) (i) Effective date of filing of Pharmaquest/Sandoz LTD. IND - June 6, 1983.

(ii) Date of filing of Sandoz Pharmaceuticals Corporation NDA - June 30 1991.

(iii) Date of Approval of Sandoz Pharmaceuticals Corporation NDA - December 30, 1992.

(B) Span under 35 USC 156(g)(1)(B)(i) between June 6, 1983 and June 30, 1991 equals 8 years and 24 days (2946 days).

(C) Span under 35 USC 156(g)(1)(B)(ii) between June 30, 1991 and December 30, 1992 equals 1 year and 6 months (549 days).

(D) (i) Number of days under (B) before the date on which patent was issued equals 1856 days.

(ii) Half of 2946 days [from (B)] minus 1856 days [from (D) (i)] equals 545 days.

(E) Plus (from C) 549 days.

(F) Total: 545 days + 549 days equals 1094 days.

(G) Maximum extension allowable under 35 USC 156(g)(4)(C):

(original term of patent) - July 5, 2005
(14 years from NDA approval) - Dec. 30, 2006
Equals: 543 days

(H) The period remaining in the term of U.S. Patent 4,755,534 after NDA approval is 12 years, 6 months and 6 days which, when added to the 543 days requested by applicant, does not exceed 14 years and thus in compliance with 35 USC 156(c)(3).

13. Sandoz Ltd. acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought by this application.

14. A letter in triplicate authorizing the Commissioner of Patents and Trademarks to charge the required fee or fees for receiving and acting upon this APPLICATION FOR PATENT TERM EXTENSION UNDER 35 USC 156 to Deposit Account No. 19-0134 is being mailed on even date herewith.

15. All inqiries and correspondence relating to this application for patent term extension should be directed to:

Robert S. Honor
Patent and Trademark Affairs
Sandoz Pharmaceuticals Corporation
59 Route 10
E. Hanover, New Jersey 07936

16. The undersigned hereby certifies that a duplicate original of this application for extension is submitted herewith.

17. Attached hereto as Appendix E hereof is a Declaration as set forth in paragraph (b) of 37 CFR §1.740.

It is respectfully requested that the above Extension of the Patent Term under 35 USC 156 of U.S. Patent No. 4,755,534 be granted.

Respectfully submitted,

Carl W. Battle
Registration No. 30,731
(201) 503-8177

CWB:lmc

SANDOZ PHARMACEUTICALS CORPORATION
59 Route 10
E. Hanover, N.J. 07936

February 25, 1993

Enclosures: Appendices A, B, C, D and E

APPENDIX A

Case No. 900-9253/CIP/CONT
U.S. Patent No. 4,755,534

A S S I G N M E N T

Whereas, FIRST FIDELITY BANK, NATIONAL ASSOCIATION, NEW JERSEY, hereinafter referred to as "FIRST FIDELITY BANK, N.A." formerly First National State Bank, formerly Fidelity Union Bank/First National State, formerly Fidelity Union Bank, formerly Fidelity Union Trust Company, a corporation incorporated under the laws of New Jersey, with its registered office at 765 Broad Street, Newark, N.J., is - by assignment, pursuant to the Twenty-Third Article of the Trust Indenture of May 4, 1955, known as the Sandoz Trust, which indenture by reference is made a part hereof and is hereinafter referred to as "The Trust", dated November 18, 1981 from SANDOZ LTD. (also known as SANDOZ AG), a corporation incorporated under the laws of Switzerland, with its registered office at Basle, Switzerland, - the owner of the entire right, title and interest in and to United States Letters Patent No. 4,755,534 which issued July 5, 1988.

for PROPENYLAMINES, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND THEIR USE AS PHARMACEUTICALS

WHEREAS, pursuant to Article Six (c)(2) of the Trust, SANDOZ LTD. has the right to withdraw any part of the Trust estate during Condition I of the Trust and wherein Condition I has been since the date of indenture and is still in existence, and whereas by letter dated January 7, 1993, SANDOZ LTD. has duly authorized withdrawal from the Trust Estate of United States Letters Patent No. 4,755,534;

NOW, THEREFORE, FIRST FIDELITY BANK, N.A., the Executive Trustee in the Trust, hereby assigns said property, namely the aforesaid
United States Letters Patent No. 4,755,534

and any and all divisions, reissues, continuations and extension thereof, any and all United States Letters Patents, which may be granted therefor, to the said SANDOZ LTD.;

IN WITNESS WHEREOF, FIRST FIDELITY BANK, N.A., has caused these presents to be signed by its proper corporate officers thereunto duly authorized and its corporate seal to be hereunto affixed.

Dated this 1ST day of FEBRUARY, 1993.

FIRST FIDELITY BANK, N.A.

James D. Hahn

United States Patent [19]

Stuetz

[11] **Patent Number: 4,755,534**

[45] **Date of Patent: Jul. 5, 1988**

[54] **PROPENYLAMINES, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND THEIR USE AS PHARMACEUTICALS**

[75] Inventor: **Anton Stuetz**, Maria Enzersdorf, Austria

[73] Assignee: **Sandoz Ltd.**, Basel, Switzerland

[21] Appl. No.: **646,724**

[22] Filed: **Sep. 4, 1984**

Related U.S. Application Data

[63] Continuation of Ser. No. 233,559, Feb. 11, 1981, abandoned, which is a continuation-in-part of Ser. No. 180,207, Aug. 21, 1980, abandoned.

[30] **Foreign Application Priority Data**

Aug. 22, 1979 [CH] Switzerland 7656/79

[51] **Int. Cl.**[4] **A61K 31/135; C07C 87/28**

[52] **U.S. Cl.** **514/655**; 564/387

[58] **Field of Search** 564/387; 280/501.1; 514/645, 657, 658

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,270,056	8/1966	Martin et al.	564/387 X
4,282,251	8/1981	Berney	564/387 X
4,680,291	7/1987	Hamberger et al.	564/387 X

FOREIGN PATENT DOCUMENTS

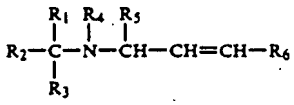
0000896	3/1979	European Pat. Off.	564/387

Primary Examiner—Robert V. Hines

Attorney, Agent, or Firm—Gerald D. Sharkin; Robert S. Honor; Thomas O. McGovern

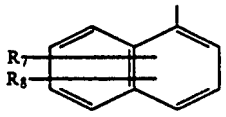
[57] **ABSTRACT**

A compound of the formula:



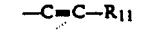
I

wherein the double bond is in the trans configuration and R_1 is a radical of formula IIa,



IIa

R_2, R_3, R_5, R_7 and R_8 are each hydrogen,
R_4 is methyl, and
R_6 is a radical of formula IIIa



IIIa

where R_{11} is n-butyl, tertiary butyl or phenyl or a chemotherapeutically acceptable acid addition salt thereof; processes for their production, their use as pharmaceuticals and pharmaceutical compositions containing them.

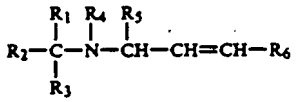
7 Claims, No Drawings

PROPENYLAMINES, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND THEIR USE AS PHARMACEUTICALS

This is a continuation of application Ser. No. 233,559, filed Feb. 11, 1981, and now abandoned which in turn is a continuation-in-part of application Ser. No. 180,207, filed Aug. 21, 1980, now abandoned.

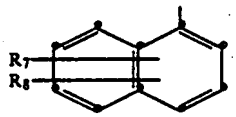
This invention relates to propenylamines, processes for their production, pharmaceutical compositions containing them and their use as pharmaceuticals.

The invention provides compounds of formula I,

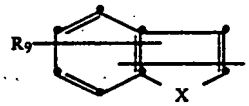


I

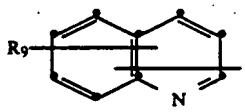
wherein (a) R_1 represents a group of formula



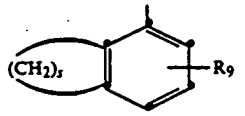
IIa



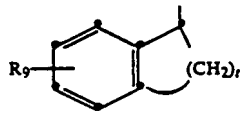
IIb



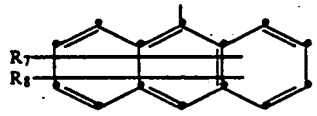
IIc



IId

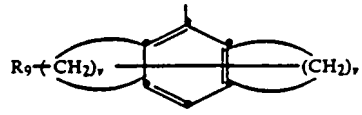


IIe



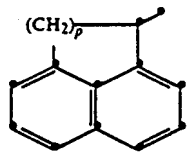
IIf

or

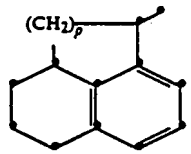


IIg

and R_2 represents hydrogen or lower alkyl, or R_1 and R_2 together represent a group of formula



IIh



IIi

whereby in the formulae IIa to IIi,

R_7 and R_8 represent, independently, hydrogen, halogen, trifluoromethyl, hydroxy, nitro, lower alkyl or lower alkoxy,

R_9 represents hydrogen, halogen, hydroxy, lower alkyl or lower alkoxy,

X represents oxygen, sulphur, imino, lower alkyl imino or a radical of formula $-(CH_2)_r-$,

p is 1, 2 or 3,

r is 1, 2 or 3,

s is 3, 4 or 5,

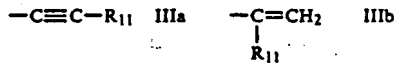
t is 2, 3 or 4, and

v is 3, 4, 5 or 6;

R_3 and R_5 represent, independently, hydrogen or lower alkyl, and

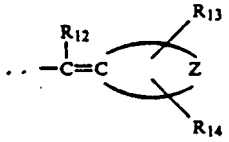
R_4 represents C_{1-6}alkyl or C_{3-8}cycloalkyl-(C_{1-6})-alkyl; and

R_6 represents a group of formula



IIIa IIIb

or



IIIc

wherein

R_{11} represents hydrogen, optionally α-hydroxy substituted alkyl; alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, phenyl, phenalkyl or thienyl,

R_{12}, R_{13} and R_{14} represent, independently, hydrogen or lower alkyl, and

represents a C_{5-8} cycloalkylidene radical optionally containing a double bond; or

(b) R_1 represents a group of formula IIa to IIg as defined under (a),

R_2 represents hydrogen or lower alkyl,

R_3 and R_4 together form a group $-(CH_2)_u-$, wherein u is an integer of 1 to 8, and

R_5 and R_6 have the meanings given under (a).

Any lower alkyl or lower alkoxy radical has preferably 1 to 4 carbon atoms, especially 2 or 1 carbon atoms. Unless otherwise stated alkyl moieties preferably have 1

to 12 carbon atoms especially 2 to 8 carbon atoms, particularly 2 to 6 carbon atoms and most preferably 3 to 5 carbon atoms and if bridging 1 to 4 particularly 1 or 2 carbon atoms. Any alkenyl or alkynyl radical has preferably 3 to 6 carbon atoms, especially 3 to 4 carbon atoms, e.g. allyl, propenyl or propynyl. Such alkyl, alkoxy, alkenyl and alkinyl groups can be straight-chain or branched. A preferred cycloalkylidene radical is cyclohexylidene. The term cycloalkyl is to be understood as including polycyclo groups such as bornyl or adamantyl but is preferably cyclohexyl or cyclopentyl.

Conveniently R_7 and R_8 are identical and are both hydrogen. Conveniently R_9 is hydrogen or halogen. In IIb and IIc the bond to the carbon atom to which R_2 and R_3 are attached is conveniently attached meta to X and para to the ring nitrogen, respectively. X is conveniently sulphur, imino or lower alkylamino. R_1 is preferably a radical of formula IIb, IIc or IId, or especially IIa. R_2 is preferably hydrogen. R_3 is preferably hydrogen and R_4 is conveniently alkyl. R_5 is conveniently hydrogen.

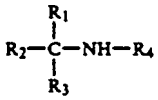
The values of p, r, s, t, u and v are conveniently chosen to produce a seven- preferably a five- or six-membered ring.

The double bond between R_6 and the nitrogen atom preferably has the trans-configuration.

Halogen stands for fluorine, chlorine or bromine, preferably chlorine or bromine.

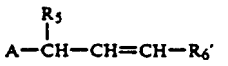
The present invention also provides a process for the production of a compound of formula I, which comprises

(a) when R_6 represents a group of formula IIIa, as defined above, (compound Ia), reacting a compound of formula IV,



IV

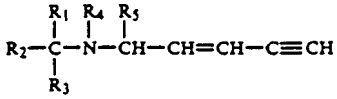
wherein
R_1 to R_4 are as defined above, with a conpound of formula V,



V

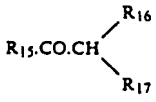
wherein
A is a leaving group, R_5 is as defined above, and
R_6' stands for a group of formula IIIa, as defined above, or

(b) when R_6 represents a group of formula IIIa, wherein R_{11} represents α-hydroxyalkyl (compounds Ib), reacting a metalated compound of formula Ic,



Ic

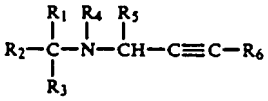
wherein R_1 to R_5 are as defined above, with a carbonyl compound of formula VII,



VII

wherein R_{15}, R_{16} and R_{17} represent independently hydrogen or lower alkyl, or

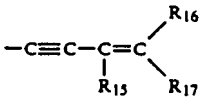
(c) when the double bond between R_6 and the nitrogen atom is in trans configuration (compounds Id) reducing a compound of formula VIII,



VIII

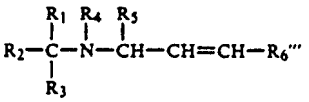
wherein R_1 to R_6 are as defined above, with diisobutylaluminumhydride, or

(d) when R_6 represents a group of IIIb or IIIc as defined above or a group of formula IIId,



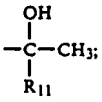
IIId

wherein R_{15}, R_{16} and R_{17} are as defined above (compounds Ie) splitting off water from a compound of formula

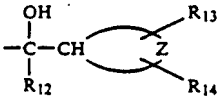


If

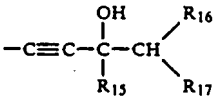
wherein
R_1 to R_5 are as defined above, and
R_6''' represents a group of formula IIIe, IIIf, or IIIg,



IIIe



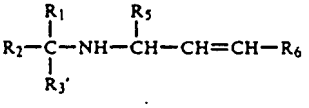
IIIf



IIIg

wherein
R_{11} to R_{17} and Z are as defined above, or

(e) when R_3 represents hydrogen or lower alkyl and R_4 represents C_{1-6}alkyl or C_{3-8}cycloalkyl-(C_{1-6})-alkyl (compounds Ig), introducing the group R_4' into a compound of formula IX,



IX

wherein
R_1, R_2, R_5 and R_6 are as defined above,
R_3' represents hydrogen or lower alkyl, and
R_4' represents C_{1-6}alkyl or C_{3-8}cycloalkyl-(C_{1-6})-alkyl.

Process (a) may be effected in conventional manner for the production of tertiary amines by condensation from analogous starting materials. The process may be effected in an inert solvent such as a lower alkanol, e.g. ethanol, optionally in aqueous admixture, an aromatic hydrocarbon solvent, e.g. benzene or toluene, a cyclic ether, e.g. dioxane or a carboxylic acid dialkylamide solvent, e.g. dimethylformamide. The reaction temperature is conveniently from room temperature to the boiling temperature of the reaction mixture, preferably room temperature. The reaction is conveniently effected in the presence of an acid binding agent, such as an alkali metal carbonate, e.g. sodium carbonate. The leaving group A is conveniently iodine or preferably chlorine or bromine, or an organic sulphonyloxy group having 1 to 10 carbon atoms, e.g. alkylsulphonyloxy, preferably having 1 to 4 carbon atoms such as mesyloxy, or alkylphenylsulphonyloxy preferably having 7 to 10 carbon atoms such as tosyloxy.

Process (b) may be effected in conventional manner, for example by metalating the compound of formula Ic, e.g. with butyllithium in an inert solvent such as an ether e.g. tetrahydrofuran and subsequently reacting the metalated compound of formula Ic, thus obtained, preferably without isolation with a compound of formula VII.

The reduction with diisobutylaluminium hydride (DIBAH) according to process (c) is preferably carried out in an inert solvent e.g. in an aromatic hydrocarbon such as toluene or benzene and at room temperature or raised temperature e.g. 35° to 40° C.

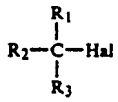
The splitting-off of water according to process (d) can be carried out with a suitable agent such as an inorganic acid, e.g. hydrochloric or sulphuric acid, an organic acid, e.g. methanesulphonic acid, bezenesulphonic acid or p-toleuensulphonic acid or an inorganic or organic acid anhydride or -halide e.e. $POCl_3$ in an inert solvent. An excess of an acid halide if used can act as reaction medium whereby the reaction is carried out in the presence of an acid binding agent such as a tertiary amine, e.g. a trialkylamine or pyridine. Reaction temperatures vary according to reaction conditions and lie for example between −10° and 180° C. The splitting-off of water can also be carried out with the help of polyphosphoric acid at temperatures between 80° and 120° C. whereby inorganic acids such as phosphoric acid, organic acids such as acetic acid or an excess of polyphosphoric acid can serve as solvent.

Process (e) may be effected in manner conventional for the "alkylation" or secondary amines (the term "alkylation" being used here to denote introduction of any of the hydrocarbyl groups R_4), for example by direct "alkylation" with an "alkylating" agent, for example a halide or sulphate, or by reductive alkylation, in particular by reaction with an appropriate aldehyde and subsequent or simultaneous reduction,. Reductive "alkylation" is suitably effected by reacting a compound of formula IX in an inert organic solvent, such as a lower alkanol, e.g. methanol, and at an elevated temperature, in particular at the boiling temperature of the reaction mixture with the corresponding aldehyde. The subsequent reduction may be effected with, for example, a complex metal hydride reducing agent, e.g. $NaBH_4$ or $NaCNBH_3$. The reduction may also be effected simultaneously to the alkylation, for example by use of formic acid which may serve both as reducing agent and as a reaction medium. The reaction is preferably carried out at raised temperature, in particular at the boiling point of the reaction mixture.

Free base forms of the compounds of formula I may be converted into salt forms and vice versa. Suitable acid addition salts are e.g. hydrochloride, hydrogen fumarate or naphthaline-1,5-disulphonate.

The compounds of the formula I and their intermediates can be obtained in the form of isomeric mixtures of the various cis/trans isomers which can be separated according to established methods. Alternatively, isomers of the compounds can be obtained by using the appropriate isomer of the starting material. Unless otherwise stated the compounds are always to be understood as being mixtures of these isomers.

The starting materials of formula IV are in part new and can be prepared by reacting in conventional manner a compound of formula X,



X

with a compound of formula XI,

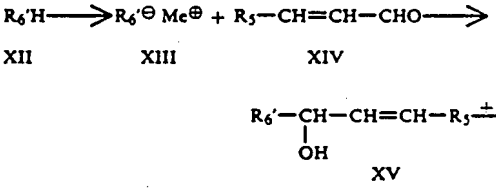
$$R_4—NH_2 \qquad XI$$

wherein in the formulae X and XI R_1 to R_4 are as defined above and Hal stands for halogen.

The starting materials of formula V are in part new and can be prepared by reacting a compound of formula XII,

$$R_6'H \qquad XII$$

according to the following scheme



XII XIII XIV

XV

whereby R_6', R_5 and A are as defined above and $Me^{\oplus}$ represents a metal cation.

The starting materials of formula VIII are new and can be prepared (a') by subjecting a compound of formula IV, defined above, and compounds of formulae XVI and XVII

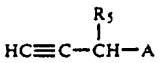
$$HC{\equiv}C—R_6 \qquad XVI$$

and

$$R_5CHO \qquad XVII$$

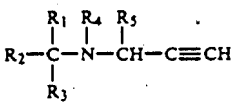
to a Mannich reaction or

(b') in the case when R_6 represents a group of formula IIIa as defined above by reacting a compound of formula IV as defined above with a compound of formula XVIII



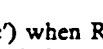
XVIII

to give a compound of formula XIX,



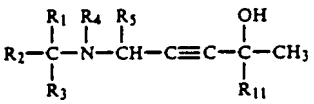
XIX

and subjecting this to a Cadiot-Chodkiewicz coupling reaction with Cu^+ and a compound of formula XX,



XX

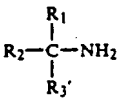
or (c') when R_6 represents a group of formula IIIb as defined above splitting off water from a compound of formula XXI,



XXI

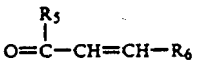
whereby in the formulae XVI to XXI R_1 to R_6, R_6', R_{11}, A and Hal are as defined above.

The starting materials of formula IX are new and can be prepared for example by reacting a compound of formula XXII,



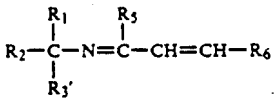
XXII

with a compound of formula XXIII



XXIII

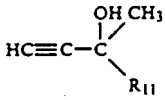
to give a compound of formula XXIV



XXIV

and reducing the e.g. with a complex hydride such as $NaBH_4$, whereby in the formulae XXII to XXIV R_1, R_2, R_3', R_5 and R_6 are as defined above.

Compounds of formula XXI can be prepared (a'') by subjecting a compound of formula IV as defined above, a compound of formula XVII as defined above, and a compound of formula XXV,



XXV

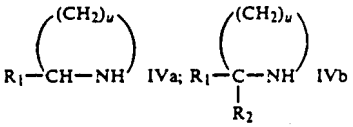
to a Mannich reaction, or

(b'') metalating a compound of formula XIX, as defined above, and reacting the metal compound thus obtained with a carbonyl compound of formula XXVI,

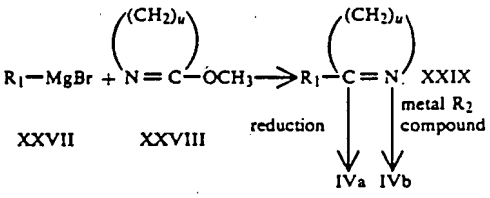
XXVI

whereby in the formulae XXV and XXVI R_{11} is as defined above.

The compounds of formulae IVa and IVb



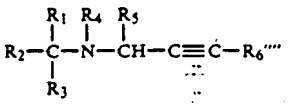
can be prepared according to the following scheme



XXVII XXVIII XXIX IVa IVb

whereby in the formulae IVa, IVb and XXVII to XXIX R_1, R_2 and u are as defined above.

The starting materials of formula If wherein R_6''' represents a group of formula IIIe or IIIf as defined above are new and can be prepared by reduction with $LiAlH_4$ of a compound of formula XXIa,



XXIa

wherein R_1 to R_5 are as defined above and R_6'''' represents a group of formula IIIe or IIIf as defined above.

Compounds of formula XX are in part new and can be prepared by reacting a compound of formula XII, as defined above, with butyllithium and a halogen.

The new compounds of formulae IV, V, VIII, IX XX and If also form part of the invention. The remaining intermediate compounds are either known or can be prepared according to known methods or as hereinbefore described.

The compounds of formula I are useful because they possess chemotherapeutic activity. In particular, they are useful as antimycotic agents, as indicated in vitro in various families and types of mycetes, including Trichophyton spp, Aspergillus spp, Microsporum spp and Sporotrychium schenkii and Candida spp at concentrations of, for example 0.01 to 100 μg/ml, and in vivo in the experimental skin mycosis model in guinea pigs. In this model, guinea pigs are infected by subcutaneous applications of Trichophyton Quinckeanum. The test substance is administered daily for 7 days beginning 24 hours after the infection either by local application by rubbing the test substance (taken up in polyethylene glycol) on the skin surface, or perorally or sub-cutaneously, the test substance being administered as a suspension. The activity is shown on local application at concentrations of for example 0.01 to 5%. The oral activity is shown in vivo in the guinea pig—Trichophytosis model at dosages of, for example 2 to 70 mg/kg.

For the above-mentioned use, the dose administered will of course vary depending on the compound employed, mode of administration and treatment desired. However, in general, satisfactory results are obtained

when administered at a daily dosage of from 1 to 100 mg/kg of animal body weight, conveniently given in divided doses two to four times daily, or in sustained release form. For the larger mammals, the corresponding daily dosages are in the range of from 70 to 2000 mg, and dosage forms suitable for oral administration comprise from 17.5 to 1000 mg. The invention therefore also concerns a method of treating diseases or infections caused by mycetes using a compound of formula I.

The compounds may be used in free base form or in the form of chemotherapeutically acceptable acid addition salts. Such salt forms exhibit the same order of activity as the free base forms. Suitable salt forms are e.g. hydrochloride, hydrogen fumarate or napththaline-1,5-disulphonate.

The compounds may be admixed with conventional chemotherapeutically acceptable diluents and carriers, and, optionally, other excipients and administered in such forms as tablets or capsules. The compounds may alternatively be administered topically in such conventional forms as ointments or creams or parenterally. The concentrations of the active substance will of course vary depending on the compound employed, the treatment desired and the nature of the form etc. In gereral, however, satisfactory results are obtained e.g. in topical application forms at concentrations of from 0.05 to 5, in particular 0.1 to 1 wt %.

Such compositions also form part of the invention.

Examples of preferred compound groups are

(i) compounds of formula I wherein R_6 represents a group of formula IIIa wherein R_{11} represents alkyl preferably C_2–C_8alkyl, more preferably C_2–C_6alkyl, most preferably C_3–C_5alkyl for example n- or in particular t-butyl;

(ii) compounds of formula I wherein R_6 represents a group of formula III wherein R_{11} represents α-hydroxy substituted alkyl; alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, phenyl, phenalkyl or thienyl;

(iii) compounds of formula I wherein R_{11} represents alkyl, alkenyl, alkynyl, cycloalkylalkyl, phenyl or phenalkyl and all other substituents are as defined under formula I;

(iv) compounds of formula I wherein

(a)

R_1 represents a group of the formula IIa, IIb, IIe,
R_2 represents hydrogen,
R_3 represents hydrogen,
R_4 represents lower alkyl,
R_5 represents hydrogen or lower alkyl, or
R_3 and R_4 together form a group $—(CH_2)_u—$ or

(b) wherein

R_1 and R_2 together represent a group of the formula IIh,
R_3 represents hydrogen,
R_4 represents lower alkyl,
R_5 represents lower alkyl and
R_6 is as hereinbefore defined,

whereby within these groups R_6 is preferably a group of formula IIIa as hereinbefore defined or as described under (i) or (ii) above and/or R_1 is preferably a group of formula IIa.

Preferred meanings of the substituents in the compounds of the formula I are such as set out hereinbefore.

Compounds of formula I are generally preferred wherein the double bond between R_6 and the nitrogen atom is in trans-configuration.

Particularly preferred individual compounds are: N-methyl-N-(1-naphthylmethyl)-non-2(trans)-en-4-ynyl-1-amine and N-methyl-N-(1-naphthylmethyl)-6,6-dimethyl-hept-2(trans)-en-4-ynyl-1-amine, and their hydrochlorides.

The following Examples illustrate the invention whereby all temperatures are in degrees centigrade.

EXAMPLE 1

trans-N-(3-Benzo[b]thiophenemethyl)-N-methyl-non-2-en-4-ynyl-1-amine and
cis-N-(3-Benzo[b]thiophenemethyl)-N-methyl-non-2-en-4-ynyl-1-amine [process (a)]

12 g 1-Bromo-2-nonen-4-yne (cis/trans mixture) are added dropwise to a mixture of 10.5 g N-(3-Benzo[b]thiophenemethyl)-N-methylamine, 8.2 g K_2CO_3 and 100 ml dimethylformamide and stirred overnight. The reaction mixture is filtered and the solvent removed under vacuum. The residue is partitioned between ether and saturated aqueous $NaHCO_3$, the organic phase dried, concentrated under vacuum and chromatographed over kieselgel using toluene/ethylacetate 4:1 as eluant. The trans isomer is eluted first followed by the cis isomer. Both are oils.

EXAMPLE 2

trans-N-Methyl-N-(1-naphthylmethyl)-6-hydroxy-6-methyl-hept-2-en-4-ynyl-1-amine [process (b)]

10.7 ml of a 15% butyllithium solution in hexane are added dropwise to 3 g of trans N-methyl-N-(1-naphthylmethyl)pent-2-en-4-ynyl-1-amine in absolute tetrahydrofuran and reacted after 30 minutes with a solution of 1.79 g of acetone. The reaction mixture is stirred for 24 hours at room temperature, poured onto ice and extracted with chloroform. The organic phase is washed, dried and concentrated under vacuum. After chromatography over kieselgel (eluant toluene/ethyl acetate 4:1) the title compound is obtained as an oil.

EXAMPLE 3

(a)

trans-N-Methyl-N-(1-naphthylmethyl)-non-2-en-4-ynyl-1-amine [process (c)]

72 ml of a 1.2M solution of DIBAH in toluene are added dropwise to a solution of 5 g N-methyl-N-(1-naphthylmethyl)-2,4-nonadiynyl-1-amine in dry toluene and the resulting mixture stirred under protective gas overnight at 40° and then for 24 hours at room temperature.

The excess reagent is broken down with 2N NaOH under cooling and the reaction mixture extracted with ether. The organic phase is dried, concentrated under vacuum and chromatographed over kieselgel (eluant—toluene/ethylacetate 95:5). The title substance is isolated as an oil.

(b) Hydrochloride salt

The compound from (a) is converted to its hydrochloride in conventional manner e.g. by treating with 4N ethanolic HCl and melts after recrystallisation at 118°–121° C.

EXAMPLE 4

N-Methyl-N-(1-naphthylmethyl)-deca-2-(trans),6(cis)-dien-4-ynyl-1-amine

1 g trans-N-Methyl-N-(1-naphthylmethyl)-6-hydroxy-dec-2-en-4-ynyl-amine are refluxed under a water separator with 570 mg p-toluenesulphonic acid (monohydrate) in

benzene. The mixture is cooled after 2 hours, the organic phase shaken a number of times with saturated aqueous $NaHCO_3$, dried and concentrated under vacuum. The residue is chromatographed over kieselgel (eluant—toluene/ethylacetate 9:1) to give the title product.

EXAMPLE 5

N-Methyl-N-(1-naphthylmethyl)-4-cyclohexyl-2-(trans)-4-pentadienyl-1-amine (A) and N-Methyl-N-(1-naphthylmethyl)-4-cyclohexylidenyl-2-(trans)-pentenyl-1-amine (B)

1 g N-Methyl-N-(1-naphthylmethyl)-4-hydroxy-4-cyclohexyl-2-pentenyl-1-amine is refluxed under a water separator with 570 mg p-toluenesulphonic acid (monohydrate) in benzene. The mixture is cooled after 2 hours, the organic phase shaken a number of times with saturated aqueous $NaHCO_3$, dried and concentrated under vacuum. The residue is chromatographed over kieselgel (eluant—toluene/ethyl acetate 9:1) to obtain first title product (A) followed by title product (B) as oils.

EXAMPLE 6

trans-N-Methyl-N-(1-naphthylmethyl)-4-cyclohexylidenyl-2-buten-yl-amine [process (e)]

3 g (1-Naphthylmethyl)amine and 2.86 g 4-cyclohexylidenyl-2-butenal are stirred in ether together with a 4 Å molecular sieve. The reaction mixture is filtered and concentrated under vacuum. The residue is taken up in methanol, treated with 800 mg $NaBH_4$ and stirred for 2 hours at room temperature.

The reaction mixture containing the secondary amine thus obtained is taken directly for reductive methylation. 8 ml 37% aqueous formaldehyde solution are added and refluxed for 1 hour. The mixture is then treated under ice-cooling with 3.6 g $NaBH_4$ and stirred for 16 hours at room temperature. The resulting mixture is concentrated under vacuum, the residue partitioned between saturated $NaHCO_3$ and ethyl acetate and the organic phase dried and concentrated. The title substance is obtained by chromatography over kieselgel (eluant—toluene/ethyl acetate 4:1) as an oil.

The following compounds of formula I can be obtained in an analogous manner.

TABLE I

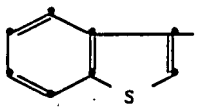
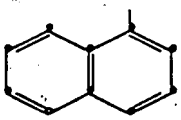
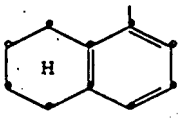
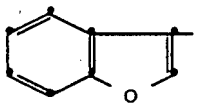
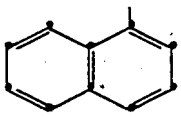
Example	R_1	R_2	R_3	R_4	R_5	R_6	Conf.	Physical data	Proc.
7		H	H	CH_3	H	$-C\equiv C-(CH_2)_3-CH_3$	trans	oil	c, e
8	"	H	H	CH_3	H	"	cis	oil	e
9		H	H	CH_3	H	"	cis	oil	a, e
10		H	H	CH_3	H	"	trans	oil	a,c,e
11	"	H	H	CH_3	H	"	cis	oil	a, e
12		H	H	CH_3	H	"	trans	oil	a,c,e
13	"	H	H	CH_3	H	"	cis	oil	a, e
14		H	H	CH_3	H	$-C\equiv CH$	trans	mp (hydrochloride) 150–155°	a,c,e
15	"	H	$R_3 + R_4 + N$		H	"	trans	mp (hydrochloride) 150–155°	a,c
16	"	H	H	CH_3	H	$-C\equiv C-C(CH_3)_3$	trans	m.p. (hydrochloride)	a,c,e

TABLE I-continued

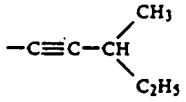
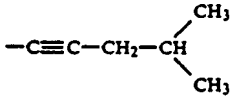
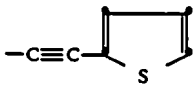
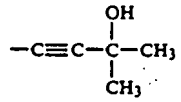
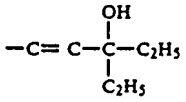
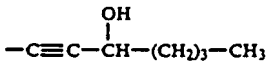
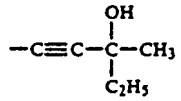
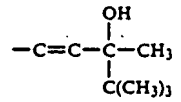
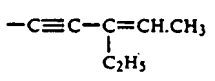
Example	R_1	R_2	R_3	R_4	R_5	R_6	Conf.	Physical data	Proc.
								199–202° (crystal invertion above 135°)	
17	"	H	H	CH_3	H	"	cis	oil	a, e
18	"	H	H	CH_3	H	$-C\equiv C-C_6H_5$	trans	oil	a,c,e
19	"	H	H	CH_3	H	"	cis	oil	a, e
20	"	H	H	CH_3	H		trans	m.p. (hydro-chloride) 160–162°	a,c,e
21	"	H	H	CH_3	H	"	cis	oil	a,e
22	"	H	H	CH_3	H		trans	m.p. (hydro-chloride) 124–126°	a,c,e
23	"	H	H	CH_3	H	"	cis	oil	a, e
24	"	H	H	CH_3	H		trans	oil	a,c,e
25	"	H	H	CH_3	H		trans	oil	c,e
26	"	H	H	CH_3	H		trans	oil	b,c,e
27	"	H	H	CH_3	H		trans	oil	b,c,e
28	"	H	H	CH_3	H		trans	oil	b,c,e
29	"	H	H	CH_3	H		trans	oil	b,c,e
30	"	H	H	CH_3	H	$-C\equiv C-(CH_2)_3-CH_3$	trans	mp (hydro-chloride) 118–121°	a, e
31	"	H	H	CH_3	H	$-C\equiv C-(CH_2)_2-CH_3$	trans	oil	a,c,e
32	"	H	H	CH_3	H	$-C\equiv C-(CH_2)_4-CH_3$	trans	oil	a,c,e
33	"	H	H	CH_3	H	$-C\equiv C-(CH_2)_5-CH_3$	trans	oil	a,c,e
34	"	H	$R_3 + R_4 + N$		H	$-C\equiv C-(CH_2)_2-CH_3$	trans	oil	a,c
35	"	H	"		H	$-C\equiv C-(CH_2)_3-CH_3$	trans	oil	a,c
36	"	H	H	CH_3	H	$-C\equiv C-CH=CH-(CH_2)_2-CH_3$	trans	oil	a,c,e
37	"	H	H	CH_3	H		trans	oil	a,c,d e

TABLE I-continued

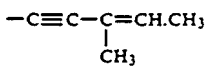
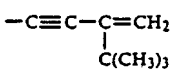
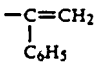
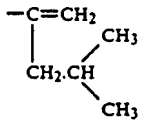
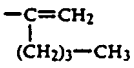
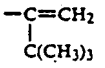
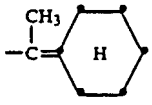
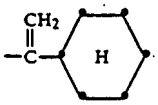
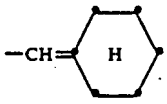
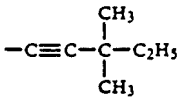
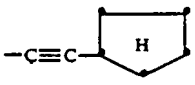
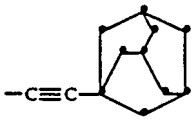
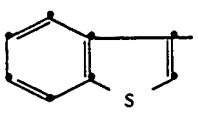
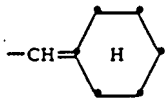
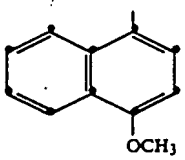
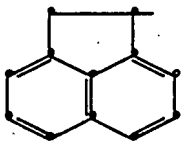
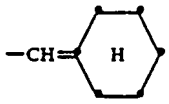
Example	R_1	R_2	R_3	R_4	R_5	R_6	Conf.	Physical data	Proc.
38	"	H	H	CH_3	H		trans	oil	a.c.d e
39	"	H	H	CH_3	H		trans	oil	a.c.d e
40	"	H	H	CH_3	H		trans	oil	c.d. e
41	"	H	H	CH_3	H		trans	oil	c.d. e
42	"	H	H	CH_3	H		trans	oil	c.d. e
43	"	H	H	CH_3	H		trans	oil	c.d. e
44	"	H	H	CH_3	H		trans	oil	c.e
							trans	oil	c.e
45	"	H	H	CH_3	H		trans	oil	c.d
46	"	H	H	CH_3	H	$-C\equiv C-CH_2OH$	trans	oil	b.c.e
47	"	H	H	CH_3	CH_3	$-C\equiv C-(CH_2)_3-CH_3$	trans	oil	a.c.e
48	"	H	H	CH_3	CH_3	"	cis	oil	a.e
49	"	H	H	CH_3	H		trans	oil	a.c.e
50	"	H	H	CH_3	H	"	cis	oil	a.e
51	"	H	H	CH_3	H		trans	oil	a.c.e
52	"	H	H	CH_3	H	"	cis	oil	a.c
53	"	H	H	CH_3	H		trans	oil	a.c.e
54	"	H	H	CH_3	H	"	cis	oil	a.e
55		H	H	CH_3	H		trans	oil	c.d.e

TABLE I-continued

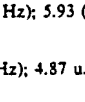
Example	R_1	R_2	R_3	R_4	R_5	R_6	Conf.	Physical data	Proc.
56		H	H	CH_3	H	$-C\equiv C-C(CH_3)_3$	cis	oil	a.c.e
57	"	H	H	CH_3	H	"	cis	oil	a.e
58	$R_1 + R_2$ 		H	CH_3	H		trans	oil	c.d.e
59	"		H	CH_3	H	$-C\equiv C-C(CH_3)_3$	trans	oil	a.c.e

In the following table NMR data are given. Data comprises peaks in ppm relative to TMS as standard in $CDCL_3$. Types of peaks are

m=multiplet
dt =double triplet
dm=double multiplet
s=singlet
d=doublet
t=triplet
ps.t=pseudo triplet
dd=double doublet
dbr=double broad
br=broad
qua=quartet
mbr=multiple broad
sext=sextuplet
ddd=double double doublet
sbr=single broad

Example	Isomer	Spectrum
1,7	trans	δ = 7.7–8.0 (m, 2H); 7.15–7.45 (m, 4H); 6.14 (dt, J=16 and 2 × 6.5 Hz, 1 olef. H); 6.65 (dm, J=16 Hz, 1 olef. H); 3.72 (s, 2H); 3.10 (d, J=6.5 Hz, 2H); 2.3 (m, 2H); 2.24 (s, 3H); 1.2–1.7 (m, 4H); 0.9 (ps.t., 3H).
1,8	cis	δ = 7.7–8.0 (m, 2H); 7.15–7.45 (m, 4H); 6.0 (dt, J=11 and 2 × 6.5 Hz, 1 olef. H); 5.64 (dm, J=11 Hz, 1 olef. H); 3.66 (s, 2H); 3.35 (d, J=6.5 Hz, 2H); 2.34 (m, 2H); 2.28 (s, 3H); 1.2–1.7 (m, 4H); 0.9 (ps.t., 3H).
9	cis	δ = 8.2–8.4 (m, 1H); 7.7–7.9 (m, 2H); 7.3–7.6 (m, 4H); 6.05 (dt, J=10.8 + 2 × 7 Hz, 1 olef. H); 5.65 (dm, J=10.8 Hz, 1 olef. H); 3.92 (s, 2H); 3.38 (dd, J=7 u. 1.5 Hz, 2H); 2.34 (m, 2H); 2.25 (s, 3H); 1.2–1.8 (m, 4H); 0.94 (m, 3H).
10	trans	δ = 6.9–7.2 (m, 3H); 6.12 (dt, J=16 and 2 × 6.5 Hz, 1 olef. H); 5.64 (dm, J=16 Hz, 1 olef. H); 3.4 (s, 2H); 3.05 (d, J=6.5 Hz, 2H); 2.7–2.9 (m, 4H); 2.2–2.4 (m, 2H); 2.18 (s, 3H); 1.65–1.9 (m, 4H); 1.3–1.7 (m, 4H); 0.92 (m, 3H).
11	cis	δ = 6.85–7.2 (m, 3H); 5.97 (dt, J=11 and 6.5 Hz, 1 olef. H); 5.60 (dm, J=11 Hz, 1 olef. H); 3.45 (s, 2H); 3.30 (d, J=6.5 Hz, 2H); 2.7–2.9 (m, 4H); 2.2–2.4 (m, 2H); 2.22 (s, 3H); 1.7–1.9 (m, 4H); 1.3–1.7 (m, 4H); 0.95 (m, 3H).
12	trans	δ = 7.1–7.8 (m, 5H); 6.14 (dt, J=16 and 2 × 6.5 Hz, 1 olef. H); 5.65 (dm, J=16 Hz, 1 olef. H); 3.63 (s, 2H); 3.1 (d, J=6.5 Hz, 2H); 2.2–2.4 (m, 2H); 2.25 (s, 3H); 1.2–1.7 (m, 4H); 0.9 (m, 3H).
13	cis	δ = 7.1–7.8 (m, 5H); 6.0 (dt, J=11 and 2 × 6.5 Hz, 1 olef. H); 5.64 (dm, J=11 Hz, 1 olef. H); 3.66 (s, 2H); 3.35 (d, J=6.5 Hz, 2H); 2.2–2.4 (m, 2H); 2.30 (s, 3H); 1.2–1.7 (m, 4H); 0.9 (m, 3H).
16	trans	δ = 8.2–8.35 (m, 1H); 7.7–7.9 (m, 2H); 7.3–7.6 (m, 4H); 6.18 (dt, J=17 and 2×7 Hz); 5.65 (dm, J=17 Hz, 1H); 3.9 (s, 2H); 3.12 (dd, J=7 u. 1 Hz, 2H); 2.22 (s, 3H); 1.25 (s, 9H).
17	cis	δ = 8.2–8.35 (m, 1H); 7.7–7.9 (m, 2H); 7.3–7.6 (m, 4H); 6.03 (dt, J=11 and 2 × 6.5 Hz, 1H); 5.65 (dbr, J=11 Hz, 1H); 3.92 (s, 2H); 3.38 (d, J=6.5 Hz, 2H); 2.26 (s, 3H); 1.27 (s, 9H).
18	trans	δ = 8.2–8.35 (m, 1H); 7.7–7.9 (m, 2H); 7.2–7.6 (m, 9H); 6.36 (dt, J=16 and 2 × 6.5 Hz, 1H); 5.9 (dm, J=16 Hz, 1H); 3.94 (s, 2H); 3.22 (d, J=6.5 Hz, 2H); 2.28 (s, 3H).
19	cis	δ = 8.2–8.4 (m, 1H); 7.7–7.9 (m, 2H); 7.2–7.6 (m, 9H); 6.20 (dt, J=11 and 2 6.5 Hz, 1H); 5.85 (d, J=11 Hz, 1H); 3.98 (s, 2H); 3.50 (d, J=6.5 Hz, 2H); 2.30 (s, 3H).
20	trans	δ = 8.2–8.4 (m, 1H); 7.7–7.9 (m, 2H); 7.3–7.6 (m, 4H); 6.20 (dt, J=16 and 2 × 6.5 Hz, 1H); 5.80 (dm, J=16 Hz, 1H); 3.90 (s, 2H); 3.14 (d, J=6.5 Hz, 2H); 2.5 (m, 1H); 2.24 (s, 3H); 1.2–1.7 (m, 2H); 1.18 (d, J=7 Hz, 3H); 1.0 (t, J=7 Hz, 3H).
21	cis	δ = 8.2–8.4 (m, 1H); 7.7–7.9 (m, 2H); 7.3–7.6 (m, 4H); 6.05 (dt, J=11 and 2 × 6.5 Hz, 1H); 5.67 (dm, J=11 Hz, 1H); 3.94 (s, 2H); 3.40 (d, J=6.5 Hz, 2H); 2.55 (m, 1H); 2.28 (s, 3H); 1.2–1.8 (m, 2H); 1.20 (d, J=7 Hz, 3H); 1.02 (t, J=7 Hz, 3H).
22	trans	δ = 8.2–8.35 (m, 1H); 7.65–7.9 (m, 2H); 7.3–7.6 (m, 4H); 6.20 (dt, J=16 and 2 × 6.5 Hz, 1H); 5.68 (dm, J=16 Hz, 1H); 3.88 (s, 2H); 3.13 (d, J=6.5 Hz, 2H); 2.22 (s, 3H); 2.2 (m, 2H); 1.6–2.1 (m, 1H); 1.0 (d, J=7 Hz, 6H).
23	cis	δ = 8.2–8.4 (m, 1H); 7.7–7.9 (m, 2H); 7.3–7.6 (m, 4H); 6.04 (dt, J=12 and 2 × 7 Hz, 1H); 5.65 (dbr, J=12 Hz, 1H); 3.90 (s, 2H); 3.38 (d, J=7 Hz, 2H); 2.24 (s, 3H); 2.2 (m, 2H); 1.6–2.0 (m, 1H); 1.0 (d, J=7 Hz, 6H).

-continued

Example	Isomer	Spectrum
24	trans	δ = 8.2–8.4 (m, 1H); 7.65–7.9 (m, 2H); 7.3–7.6 (m, 4H); 7.15–7.3 (m, 2H); 6.95 (m, 1H); 6.36 (dt, J=16 u. 2 × 6 Hz, 1H); 5.9 (dbr, J=16 Hz, 1H); 3.92 (s, 2H); 3.20 (d, J=6 Hz, 2H); 2.28 (s, 3H).
3,30	trans	δ = 8.2–8.35 (1 arom. H); 7.7–7.9 (2 arom. H); 7.3–7.6 (4 arom. H); 6.17 (dt, 1 olef. H, J=16 + 2 × 6.5 Hz); 5.67 (d, 1 olef. H, J=16 Hz); 3.89 (s, 2H); 3.13 (d, 2H, J=6.5Hz); 2.21 (s, 3H); 2.2–2.4 (m, 2H); 1.2–1.8 (4H); 0.8–1.05 (m, 3H).
31	trans	identical with Ex. 3,30 except: δ = 2.28 (t, 2H); 1.55 (sext., 2H); 1.0 (t, 3H).
32	trans	identical with Ex. 3,30 except: δ = 1.2–1.8 (m, 6H).
33	trans	identical with Ex. 3,30 except: δ = 1.2–1.8 (m, 8H).
34	trans	δ = 8.5 (br, 1H); 7.3–7.9 (m, 6H); 6.02 (ddd, J=5, 8 + 16 Hz, 1H); 5.46 (dbr, J=16 Hz, 1H); 3.80 (br, 1H); 3.1–3.35 (m, 2H); 2.52 (dd, 8 + 14 Hz, 1H); 2.0–2.35 (m, 3H); 1.6–2.0 (m, 6H); 1.54 (sext., J=7 Hz, 2H); 0.97 (t, J=7 Hz, 3H).
35	trans	identical with Ex. 34 except: δ = 1.3–1.7 (m, 4H); 0.9 (ps.t, 3H).
4,36	trans	δ = 8.2–8.35 (m, 1H); 7.7–7.9 (m, 2H); 7.3–7.6 (m, 4H); 6.26 (dt, J=15.5 + 2× 6.5 Hz, 1H); 5.9 (dt, J=11 + 2×7 Hz); 5.85 (d, J=15.5 Hz, 1H); 5.58 (dbr, J= 11 Hz); 3.92 (s, 2H); 3.18 (d, J=6.5 Hz, 2H); 2.35 (t, 2H); 2.26 (s, 3H); 1.2–1.7 (m, 2H); 0.95 (ps.t. 3H).
37	trans	δ = 8.15–8.35 (m, 1H); 7.7–7.9 (m, 2H); 7.3–7.6 (m, 4H); 6.25 (dt, J=16 + 6 Hz, 1H); 5.86 (d, J=16 Hz, 1H); 5.70 (t, J= 7 Hz, 1H); 3.94 (s, 2H); 3.20 (d, J=6 Hz, 2H); 2.26 (s, 3H); 2.16 (qua, J=8 Hz, 2H); [1.8 (d, J=7 Hz) und 1.7 (d, J=7 Hz); Σ 3H, in ratio 6/1]; 1.06 (t, 3H).
38	trans	δ = 8.2–8.35 (m, 1H); 7.7–7.9 (m, 2H); 7.3–7.6 (m, 4H); 6.30 (dt, J=16 + 2×6 Hz, 1H); 5.86 (dJ=16 Hz, 1H); 5.75 (m, 1H); 3.92 (s, 2H); 3.18 (d, J=6 Hz, 2H); 2.26 (s, 3H); 1.87 (s, 3H); 1.8 u. 1.7 (2 d, 3H).
39	trans	δ = 8.2–8.4 (m, 1H); 7.7–7.9 (m, 2H); 7.3–7.6 (m, 4H); 6.28 (dt, J=16 + 2×6.5 Hz, 1H); 5.84 (dm, J=16 Hz, 1H); 5.30 (m, ); 3.92 (s, 2H); 3.18 (d, J=6.5 Hz, 2H); 2.26 (s, 3H); 1.18 (s, 9H).
5,44 A	trans	δ = 8.2–8.35 (1 arom. H); 7.7–7.9 (2 arom. H); 7.3–7.6 (4 arom. H); 6.22 (d, 1 olef. H, J=16 Hz); 5.93 (dt, 1 olef. H, J=16 + 2 × 6.5 Hz); 4.87 u. 4.83 (=C ); 3.90 (s, 2H); 3.19 (d, 2H, J=6.5 Hz); 2.25 (s, 3H); 1.0–2.4 (11 H, Cyclohexyl).
B	trans	δ = 8.2–8.35 (1 arom. H); 7.7–7.9 (2 arom. H); 7.3–7.6 (4 arom. H); 6.79 (d, 1 olef. H, J=16 Hz); 5.80 (dt, 1 olef. H, J=16 + 2 × 6.5 Hz); 3.92 (s, 2H); 3.24 (d, 2H, J=6.5 Hz); 2.2–2.5 (m, 4H); 2.26 (s, 3H); 1.88 (s, 3H), 1.58 (br, 6H).
40	trans	δ = 8.15–8.30 (m, 1H); 7.7–7.9 (m, 2H); 7.3–7.6 (m, 9H); 6.51 (d, J=18 Hz, 1H); 5.82 (dt, J=18 + 2 × 7.5 Hz, 1H); [5.26 (sbr, 1H) + 5.14 (d, J=2 Hz, 1H) ]; 3.88 (s, 2H); 3.20 (d, J=7.5 Hz, 2H); 2.22 (s, 3H).
41	trans	δ = 8.2–8.35 (m, 1H); 7.7–7.9 (m, 2H); 7.3–7.6 (m, 4H); 6.24 (d, J=16 Hz, 1 olef. H); 5.85 (dt, J=16 + 2 × 6.5 Hz, 1 olef. H); 4.95 (dd, J=11 + 2 Hz, 2 olef. H); 3.9 (s, 2H); 3.18 (d, J=6.5 Hz, 2H); 2.24 (s, 2H); 2.13 (d, J=6.5 Hz, 2H); 1.6–2.1 (m, 1H); 0.9 (d, J=6.5 Hz, 6H).
42	trans	δ = 8.2–8.35 (m, 1H); 7.65–7.9 (m, 2H); 7.3–7.6 (m, 4H); 6.26 (d, J=16 Hz, 1H); 5.86 (dt, J=16 + 2 × 6.5 Hz, 1H); 4.95 (s, =C); 3.90 (s, 2H); 3.18 (d, J=6.5 Hz, 2H); 2.24 (s, 3H); 2.15–2.35 (m, 2H); 1.1–1.7 (m, 4H); 0.9 (ps.t, 3H).
43	trans	δ = 8.2–8.35 (m, 1H); 7.7–7.9 (m, 2H); 7.3–7.6 (m, 4H); 6.30 (d, J=15.5 Hz, 1H); 6.02 (dt, J=15.5 Hz + 2 × 6.5 Hz, 1H); [5.07 (sbr, 1H) + 4.80 (d, J=2 Hz, 1H), =C]; 3.9 (s, 2H); 3.16 (d, 2H); 2.25 (s, 3H); 1.1 (s, 9H).
6,45	trans	δ = 8.2–8.35 (1 arom. H); 7.7–7.9 (2 arom. H); 7.3–7.6 (4 arom. H); 6.52 (dd, 1 olef. H, J=15 u. 10 Hz); 5.86 (d, 1 olef. H, J=10 Hz); 5.79 (dt, 1 olef. H, J=15 + 2 × 6.5 Hz); 3.92 (s, 2H); 3.20 (d, J= 6.5 Hz, 2H); 2.25 (s, 3H); 2.1–2.4 (m, 4H); 1.6 (br, 6H).
46	trans	δ = 8.15–8.35 (m, 1H); 7.7–7.9 (m, 2H); 7.3–7.6 (m, 4H); 6.3 (dt, J=16 + 2×6.5 Hz, 1H); 5.7 (dm, J=16 Hz, 1H); 4.34 (d, J=2 Hz, 2H); 3.9 (s, 2H); 3.16 (d, J=6.5 Hz, 2H); 2.24 (s, 3H); 2.2 (OH).
47	trans	δ = 8.2–8.35 (m, 1H); 7.65–7.9 (m, 2H); 7.3–7.5 (m, 4H); 6.17 (dd, J=16 + 7 Hz, 1H); 5.58 (dm, J=16 Hz, 1H); 3.9 (AB-System, 2H); 3.25 (m, 1H); 2.1–2.3 (m, 2H); 2.14 (s, 3H); 1.3–1.6 (m, 4H); 1.18 (d, J=7 Hz, 3H); 0.85 (m, 3H).
48	cis	δ = 8.2–8.35 (m, 1H); 7.6–7.9 (m, 2H); 7.3–7.6 (m, 4H); 5.98 (dd, J=11 + 9 Hz, 1H); 5.6 (dm, J=11 Hz, 1H); 3.96 (AB-System, 2H); 3.8 (m, 1H); 2.1–2.3 (m, 2H); 2.16 (s, 3H); 1.2–1.6 (m, 4H); 1.26 (d, J=7 Hz, 3H); 0.82 (m, 3H).
49	trans	δ = 8.15–8.35 (m, 1H); 7.6–7.9 (m, 2H); 7.3–7.6 (m, 4H); 6.14 (dt, J=16 + 2×6.5 Hz, 1H); 5.66 (dm, J=16 Hz, 1H); 3.86 (s, 2H); 3.10 (d, J=6.5 Hz, 2H); 2.2 (s, 3H); 1.4 (qua, J=7 Hz, 2H); 1.15 (s, 6H); 0.9 (t,J=7 Hz, 3H).
50	cis	δ = 8.2–8.35 (m, 1H); 7.6–7.9 (m, 2H); 7.3–7.6 (m, 4H); 6.0 (dt, J=11 + 2×6.5 Hz, 1H); 5.64 (dm, J=11 Hz, 1H); 3.9 (s, 2H); 3.35 (d, J=6.5 Hz, 2H); 2.22 (s, 3H); 1.45 (qua, J=7 Hz, 2H); 1.18 (s, 6H); 0.95 (t, J=7 Hz, 3H).
51	trans	δ = 8.15–8.35 (m, 1H); 7.6–7.9 (m, 2H); 7.3–7.6 (m, 4H); 6.16 (dt, J=16 + 2×6.5 Hz, 1H); 5.66 (dm, J=16 Hz, 1H); 3.86 (s, 2H); 3.10 (d, J=6.5 Hz, 2H); 2.7 (br, 1H); 2.2 (s, 3H); 1.4–2.1 (m, 8H).
52	cis	δ = 8.15–8.35 (m, 1H); 7.6–7.9 (m, 2H); 7.3–7.6 (m, 4H); 6.0 (dt, J=11 + 2×6.5 Hz, 1H); 5.64 (dm, J=11 Hz, 1H); 3.9 (s, 2H); 3.36 (d, J=6.5 Hz, 2H); 2.75 (br, 1H); 2.22 (s, 3H); 1.4–2.1 (m, 8H).
55	trans	δ = 7.8–8.1 (m, 2H); 7.25–7.5 (m, 3H); 6.50 (dd, J=17 + 12 Hz, 1H); 5.85 (d, J=12 Hz, 1H); 5.74 (dt, J=17 u. 2×7 Hz, 1H); 3.77 (s, 2H); 3.14 (d, J=7 Hz, 2H); 2.0–2.4 (m, 4H); 2.25 (s, 3H); 1.55 (sbr, 6H).
56	trans	δ = 8.2–8.4 (m, 2H); 7.25–7.7 (m, 3H); 6.74 (d, J=8 Hz, 1H); 6.2 (dt, J=18 + 2×7 Hz, 1H); 5.67 (dt, J=18 u. 2×15 Hz, 1H); 4.0 (s, 3H); 3.82 (s, 2H); 3.10 (dd, J=7 u. 1.5 Hz); 2.2 (s, 3H); 1.24 (s, 9H).
57	cis	δ = 8.2–8.4 (m, 2H); 7.25–7.7 (m, 3H); 6.74 (d, J=8 Hz, 1H); 6.05 (dt, J=12 + 2×7.5 Hz, 1H); 5.65 (dt, J=12 u. 2×1.5 Hz, 1H); 4.0 (s, 3H); 3.85 (s, 2H) 3.35 (dd, J=7.5 u. 1.5 Hz, 2H);

-continued

Example	Isomer	Spectrum
		2.24 (s, 3H); 1.26 (s, 9H).
58	trans	δ = 7.2–7.8 (m, 6H); 6.44 (dd, J=17 + 12 Hz, 1H); 5.80 (d, J=12 Hz, 1H); 5.66 (dt, J=17 + 2×7 Hz, 1H); 5.0 (t, J=6 Hz, 1H); 3.33 (d, J=6 Hz, 2H); 3.14 (d, J=7 Hz, 2H); 2.0–2.4 (m, 4H); 2.12 (s, 3H); 1.5 (sbr, 6H).
59	trans	δ = 7.1–7.7 (m,6H); 6.04 (dt,J=16 + 2×6.5 Hz, 1H); 5.6 (dm,J=16 Hz, 1H); 4.9 (t,J=6 Hz, 1H); 3.22 (d,J=6 Hz, 2H); 3.0 (d,J=6.5 Hz, 2H); 2.1 (s, 3H); 1.18 (s, 9H).
53	trans	δ = 8.15–8.35 (m, 1H); 7.6–7.9 (m, 2H); 7.3–7.6 (m, 4H); 6.15 (dt,J=16 + 2×6.5 Hz, 1H); 5.65 (dm, J=16 Hz, 1H); 3.85 (s, 2H); 3.10 (d, J=6.5 Hz, 2H); 2.2 (s, 3H); 1.8–2.1 (br, 9H); 1.6–1.8 (br, 6H).

The required starting materials can be obtained e.g. as follows.

1. Compounds of formula IV

(A) (3-Benzo[b]thiophenemethyl)methylamine (for Ex. 1)

3-Chloromethylbenzo[b]thiophene is dissolved in benzene, added dropwise to a ca. 10-fold excess of methylamine in ethanol at 0°–5° and then stirred for 16 hours at room temperature. The crude mixture is concentrated under vacuum, the residue partitioned between methylenechloride and 1N NaOH and the organic phase dried and evaporated under vacuum. The purified product is obtained by vacuum distillation b.p. 90°–94°/1,33 Pa.

(B) (3-Benzo[b]furanmethyl)methylamine (for Ex. 12 and 13)

Obtained analogously to Example A) b.p. 105°–110°/5.3 Pa.

(C) 2-(1-Naphthyl)piperidine (for Ex. 15, 34 and 35)

A Grignard complex is prepared by adding 43.4 g of 1-bromonaphthalene in absolute ether dropwise to 5.1 g of magnesium in 50 ml of absolute ether. The ether is removed from the reaction mixture and replaced by absolute benzene. 8 g 6-Methoxy-2,3,4,5-tetrahydropyridine are added to the boiling reaction mixture. Afte a further 8 hours the mixture is cooled, treated with saturated aqueous ammoniumchloride solution and the reaction product removed from the organic phase by shaking with aqueous HCl-solution. After neutralisation and working up the 2-(1-naphthyl)-3,4,5,6-tetrahydropyridine is dissolved directly in methanol and reduced with $NaBH_4$. After normal working up the product is converted with alcoholic HCl solution to its hydrochloride. M.p. 287°–289° (after intensive drying under high vacuum 328°–329°).

2. Compounds of formula V

(D) 1-Bromo-6,6-dimethyl-2-hepten-4-yne (for Ex. 16, 17, 56, 57 and 59)

(a) 6,6-Dimethyl-1-hepten-4-yn-3-ole:

38 ml 3,3-Dimethyl-1-butyne are dissolved in abs. tetrahydrofuran and 172 ml of a 20% solution of n-butyl-lithium added dropwise under protective gas at a temperature of −20°. The reaction mixture is then cooled to −75° and 19.3 g acrolein in 20 ml of tetrahydrofuran added dropwise. The mixture is warmed to room temperature, reacted with saturated aqueous NH_4Cl and extracted a number of times with ether. The organic phase is dried, concentrated and the purified product obtained by vacuum distillation, b.p. 70°–72°/1600 Pa.

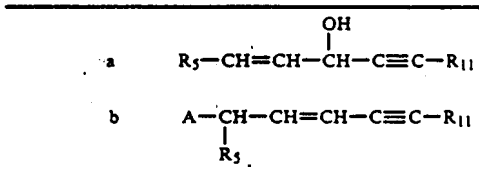
(b) 1-Bromo-6,6-dimethyl-2-hepten-4-yne:

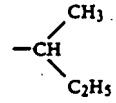
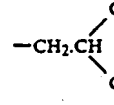
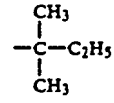
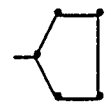
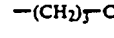
50 ml 48% HBr and 10 g PBr_3 are stirred at 40° until a homogenous mixture is obtained. An alcoholic solution of 13.5 g 6,6-dimethyl-1-hepten-4-yn-3-ole are added dropwise at 10° and stirred for 1½ hours at room temperature. The reaction mixture is poured onto ice and extracted a number of times with hexane. The organic phase is washed a number of times with aqueous NaCl, dried and concentrated. NMR-spectrography shows that the oily product comprises a 3:1 mixture of trans- and cis-1-bromo-6,6-dimethyl-2-hepten-4-yne and is taken directly for alkylation.

NMR: δ=5.5–6.4 (m, 2 olef. H), [4.15 (d. J=8 Hz) and 3.95 (d, J=8 Hz) in ratio 1:3, 2H, =CH—$\underline{CH_2}$Br], 1.20 (m, 9H).

Analogously to (D) above the following compounds of formula V can be obtained.

TABLE II



	R_{11}	R_5	A	Physical data	for Ex.
(E) a b		H	— Br	b.p. 75–80°/1460 Pa oil	20,21
(F) a b		H	— Br	b.p. 87–91°/1730 Pa oil	22,23
(G) a b		H	— Br	b.p. 90°/1460 Pa oil	49,50
(H) a b		H	— Br	b.p. 94–96°/800 Pa oil	51,52
(I) a b		CH_3	— Br	b.p. 92–93°/530 Pa oil	47,48

The remaining compounds of formula V can be obtained analogously to (D) above.

3. Compounds of formula VIII

(M) N-Methyl-N-(1-naphthylmethyl)octa-2,4-diynyl-1-amine (for Ex. 31)

9 g 1,3-Heptadiyne, 16 g methyl-(1-naphthylmethyl-)amine, 2.8 g paraformaldehyde and 1.3 g $ZnCl_2$ (anhydrous) are heated for 3 hours at 100° in absolute dioxane. After cooling the solvent is removed under vacuum, the residue partitioned between chloroform and aqueous $NaHCO_3$-solution and the organic phase dried and concentrated. The purified product is obtained by chromatography over kieselgel (toluene/ethyl acetate 9:1) as an oil.

(N) N-Methyl-N-(1-naphthylmethyl)-2,4-nonadiynyl-1-amine (for Ex. 3)

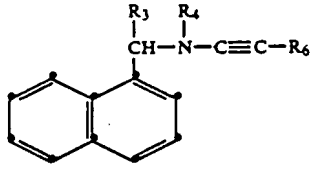
8.25 g 1-Bromohexyne are added dropwise to a mixture of 16 g N-methyl-N-(1-naphthylmethyl)-propargylamine, 0.5 g $NH_2OH.HCl$, 0.25 g CuCl and 20 ml 70% ethylamine. The reaction mixture is stirred overnight at room temperature, treated with an aqueous solution of 1 g KCN and extracted a number of times with ether. The organic phase is washed with saturated aqueous NaCl, dried and evaporated. The title substance is obtained as an oil after chromatography over Kieselgel (eluant toluene/ethyl acetate 95:5).

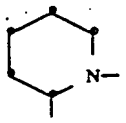
(O) N-Methyl-N-(1-naphthylmethyl)-4-t.butyl-pent-2-yn-4-enyl-1-amine (for Ex. 43)

933 mg N-Methyl-N-(1-naphthylmethyl)-4-hydroxy-4,5,5-trimethyl-2-hexynyl-1-amine are dissolved in abs. pyridine, warmed to 50° and 0.4 ml $POCl_3$ added. Stirring is carried out for one hour at 90°, the mixture poured onto ice and the reaction product isolated as an oil by extraction with ether and chromatography over kieselgel (eluant toluene/ethyl acetate 9:1).

Analogously to (M), (N) and (O) above, the following compounds of formula VIII may be obtained.

TABLE III



	R_3	R_4	R_6	Physical data	For Ex.
(P)	H	CH_3	$-C\equiv C-(CH_2)_4-CH_3$	oil	32
(Q)	H	CH_3	$-C\equiv C-(CH_2)_5-CH_3$	oil	33
(R)	H	CH_3	$-C\equiv C-C(CH_3)_3$	oil	16
(S)	$R_3 + R_4 + N$		$-C\equiv C-(CH_2)_2-CH_3$	oil	34
(T)			$-C\equiv C-(CH_2)_3-CH_3$	oil	35

The remaining compounds of formula VIII can be prepared analogously to (M), (N) and (O) above.

4. Compounds of formula If

(U) N-Methyl-N-(1-naphthylmethyl)-4-hydroxy-4-cyclohexyl-2-pentenyl-1-amine (for Ex. 5)

(a) N-Methyl-N-(1-naphthylmethyl)-4-hydroxy-4-cyclohexylpent-2-ynyl-1-amine:

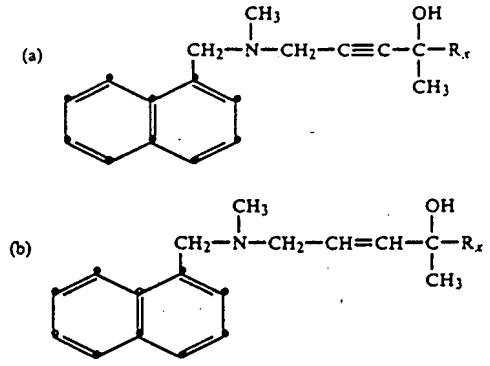
10.7 ml of a 15% solution of BuLi in hexane are added dropwise to 3 g N-methyl-N-(1-naphthylmethyl)propargyl amine in absolute tetrahydrofuran and after 30 minutes reacted with a solution of 1.79 g cyclohexylmethyl ketone. Stirring is continued for 24 hours at room temperature and the mixture poured onto ice and extracted with ether. The organic phase is washed, dried and concentrated under vacuum. Chromatography over kieselgel (eluant toluene/ethylacetate 4:1) yields the title product as an oil.

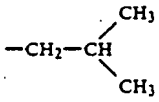
(b) N-Methyl-N-(1-naphthylmethyl)-4-hydroxy-4-cyclohexyl-2-pentenyl-1-amine:

10 g of the substance obtained under (a) are dissolved in tetrahydrofuran and added dropwise to a suspension of 1.4 g $LiAlH_4$ in abs. tetrahydrofuran and the mixture refluxed for 3 hours. Excess reagent is destroyed with ethyl acetate/H_2O. After extraction with ether, drying and evaporation under vacuum followed by chromatography over kieselgel (eluant $CHCl_3/C_2H_5OH$ 95:5) the title product is obtained as an oil.

Analogously to (U) above the following compounds can be obtained.

TABLE IV



	R_x	physical data [(a) and (b)]	For Ex.
(V) (a) (b)		oil	41
(W) (a) (b)	$-(CH_2)_3-CH_3$	oil	42
(X) (a) (b)	$-C(CH_3)_3$	oil	43
(Y) (a) (b)	$-C_6H_5$	oil	40

Compounds of formula IX can be prepared analogously to Example 6 above and are preferably taken directly without further purification or isolation for the final step.

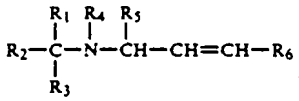
Example	Spectrum
(N)	δ = 8.2–8.35 (1 arom. H); 7.7–7.9 (2 arom. H); 7.3–7.6 (4 arom. H); 3.97 (s, 2H); 3.37 (s, 2H) 2.40 (s, 3H); 2.2.–2.4 (m, 2H); 1.2–1.8 (4H); 0.8–1.05 (m, 3H).
(M)	identical with (N) except: δ = 2.28 (t, 2H); 1.58 (sext., 2H); 1.0 (t, 3H)
(P)	identical with (N) except: δ = 1.2–1.8 (m, 6H).
(Q)	identical with (N) except: δ = 1.2–1.8 (m, 8H).
(R)	δ = 8.1–8.25 (m, 1H); 7.6–7.85 (m, 2H); 7.2–7.5 (m, 4H); 3.92 (s, 2H); 3.33 (s, 2H); 2.35 (s,3H); 1.22 (s, 9H).
(S)	δ = 8.5 (br, 1H), 7.3–7.9 (m, 6H), 4.05 (br, 1H); 3.24 (s, 2H); 3.12 (m, 1H); 2.5–2.8 (m, 1H), 2.26 (t, J=6.5 Hz, 2H); 1.6–2.0 (m, 6H), 1.56 (sext., J=7 Hz, 2H); 0.99 (t, J=7 Hz, 3H).
(T)	identical with (S) except: δ = 2.28 (ps.t, 2H); 1.3–1.7 (m, 4H); 0.91 (ps.t, 3H).
(U) (a)	δ = 8.2–8.35 (1 arom. H); 7.7–7.9 (2 arom. H); 7.3–7.6 (4 arom. H); 4.0 (s, 2H); 3.37 (s, 2H);

-continued

Example	Spectrum
	2.38 (s, 3H); 1.52 (s, 3H); 1.0–2.2 (11H).
	(b) δ = 8.2–8.35 (1 arom. H); 7.7–7.9 (2 arom.H); 7.3–7.6 (4 arom. H); 5.76 (m, 2 olef. H); 3.91 (s, 2H); 3.13 (m, 2H); 2.25 (s, 3H); 1.23 (s, 3H); 0.8–2.0 (11H).
(V)	(a) δ = 8.15–8.35 (m, 1H); 7.7–7.9 (m, 2H); 7.3–7.6 (m, 4H); 3.95 (s, 2H); 3,34 (s, 2H); 2.35 (s, 3H); 1.8–2.3 (m, 1H); 2.0 (s, OH); 1.62 (d, J=6.5 Hz, 2H); 1.53 (s, 3H); 1.04 u. 1.02 (2 d, J=6.5 Hz, Σ 6H).
	(b) δ = 8.2–8.4 (m, 1H); 7.7–7.9 (m, 2H); 7.3–7.6 (m, 4H); 5.78 (AB-portion of an ABX_2-system, 2 olef. H); 3.90 (s, 2H); 3.12 (m, 2H); 2.22 (s, 3H); 1.3–2.0 (m, 1H); 1.5 (s, OH); 1.4 (d, 2H); 1.3 (s, 3H); 0.92 u. 0.90 (2 d, J=7 Hz, Σ 6H).
(W)	(a) δ = 8.2–8.35 (m, 1H); 7.7–7.9 (m, 2H); 7.3–7.6 (m, 4H); 3.98 (s, 2H); 3.36 (s, 2H); 2.38 (s, 3H); 2.1 (br, OH); 1.2–1.9 (m, 6H); 1.56 (s, 3H); 0.95 (ps.t., 3H).
	(b) δ = 8.2–8.35 (m, 1H); 7.7–7.9 (m, 2H); 7.3–7.6 (m, 4H); 5.85 (AB-portion of an ABX_2-system, 2H); 3.90 (s, 2H); 3.12 (m, 2H); 2.25 (s, 3H); 1.2–1.7 (m, 6H + OH); 1.28 (s, 3H); 0.9 (ps.t., 3H).
(X)	(a) δ = 8.2–8.35 (m, 1H); 7.7–7.9 (m, 2H); 7.3–7.6 (m, 4H); 4.0 (s, 2H); 3.38 (s, 2H); 2.4 (s, 3H) 1.96 (br, OH); 1.54 (s, 3H); 1.14 (s, 9H).
	(b) δ = 8.2–8.4 (m, 1H); 7.65–7.9 (m, 2H); 7.3–7.6 (m, 4H); 5.6–6.1 (AB-portion of an ABX_2-system, J=15 + 2x5.5 Hz, 2H); 3.92 (s, 2H); 3.16 (d, 2H; J=5.5 Hz); 2.25 (s, 3H); 1.4 (br, OH); 1.26 (s, 3H); 0.96 (s, 9H).
(Y)	(a) δ = 8.2–8.35 (m, 1H); 7.6–7.9 (m, 4H); 7.2–7.6 (m, 7H); 4.0 (s, 2H); 3.4 (s, 2H); 2.65 (br,OH) 2.4 (s, 3H); 1.85 (s, 3H).
	(b) 8.15–8.35 (m, 1H); 7.65–7.9 (m, 2H); 7.2–7.6 (m, 9H); 5.6–6.1 (AB-portion of an ABX_2 -system, J=15 Hz + 2x5.5 Hz, 2H); 3.88 (s, 2H); 3.13 (d, J=5.5 Hz, 2H); 2.24 (s, 3H); 2.0 (s, OH); 1.65 (s, 3H).

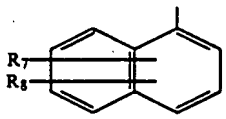
I claim:

1. A compound of the formula:



I

wherein the double bond is in the trans configuration and R_1 is a radical of formula IIa,



IIa

R_2, R_3, R_5, R_7 and R_8 are each hydrogen,
R_4 is methyl, and
R_6 is a radical of formula IIIa

IIIa

where R_{11} is n-butyl, tertiary butyl or phenyl or a chemotherapeutically acceptable acid addition salt thereof.

2. The trans compound according to claim 1 in which R_1 is 1-naphthyl, R_2 and R_3 are H; R_4 is CH_3, R_5 is H, and R_6 is —C≡C—C_6H_5.

3. N-Methyl-N-(1-naphthylmethyl)-non-2(trans)en-4-ynyl-1-amine or a chemotherapeutically acceptable acid addition salt thereof.

4. N-Methyl-N-(1-naphthylmethyl)-6,6-dimethyl-hept-2(trans)-en-4-ynyl-1-amine or a chemotherapeutically acceptable acid addition salt thereof.

5. A compound as claimed in claim 1 in the form of its hydrochloride.

6. A chemotherapeutical composition comprising an effective amount of a compound as claimed in claim 1 or a chemotherapeutically acceptable acid addition salt thereof in admixture with a chemotherapeutically acceptable diluent or carrier.

7. A method of treating diseases or infections caused by mycetes which comprises administering to a subject in need of treatment an effective amount of a compound as claimed in claim 1 or a chemotherapeutically acceptable acid addition salt thereof.

* * * * *

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

PAYOR NUMBER
001095

APPENDIX C

GERALD D. SHARKIN
SANDOZ CORP.
59 ROUTE 10
E. HANOVER, NJ 07936

PATENT AND TRADEMARK DEPT.
JAN 24 1992

DATE MAILED
01/16/92

198369

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,755,534	173	830	----	06/646,724	07/05/88	09/04/84	04	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	900-9253/CIP

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231

PTOL 435 (1V 4 88)

CHRONOLOGY OF REGULATORY ACTIVITIES

LAMISIL CREAM IND 22,218

6/06/83	IND submitted, sponsored by Pharmaquest/Sandoz Vienna
7/13/83	Letter from FDA with a FDA request for information
7/26/83	Telephone conversation with FDA to discuss 7/13/83 FDA letter
7/28/83	Amendment to IND, response to 7/13/83 FDA letter
9/08/83	Telephone conversation with FDA pharmacologist, followup for any outstanding issues
10/21/83	Amendment to IND, authorization for DMF reference submitted
12/05/83	Amendment to IND, protocol for percutaneous absorption in normal human volunteers
2/21/84	Amendment to IND, submission of final study reports for 5 tolerance studies (irritation, sensitization)
4/11/84	Letter from FDA, request for additional dermal studies
5/11/84	Amendment to IND, clinical protocols for comparison of Lamisil to clotrimazole and proposed phase II efficacy studies
5/18/84	Letter to FDA, request for meeting to review clinical and preclinical status
12/17/84	Amendment to IND, protocol for T. capitis in children
3/26/85	Amendment to IND, protocol against clotrimazole in T. versicolor
8/01/85	Letter from FDA, request for annual report
8/20/85	Amendment to IND, submission of annual report
3/05/86	Amendment to IND, protocols for Lamisil vs. placebo once a day in Candida, T. versicolor, T. corporis T. pedis (moccasin type)
5/15/86	Amendment to IND, submission of annual report and request for meeting
6/10/86	Minutes of a meeting with FDA
7/07/86	Teleconference with FDA to discuss data
9/18/86	Amendment to IND, new protocols; T. corporis/cruris, T. pedis, T. capitis
10/30/86	Amendment to IND, submission of tox findings

12/03/86 Amendment to IND, protocols submitted 9/18/86

4/20/87 Amendment to IND, submission of 52 week rat tox study

6/19/87 Amendment to IND, submission of annual report

7/28/87 Amendment to IND, submission of preclinical Juvenile tox studies

7/29/87 Amendment to IND, final report 52 week rat tox study

7/30/87 Amendment to IND, submission of proposed tox protocols

2/10/87 Amendment to IND, 3 New protocols:
1 week candidiasis
2 week T. pedis (athlete foot)
1 week T. cruris

2/16/88 Amendment to IND, preclinical safety data

2/23/88 Amendment to IND, additional preclinical safety data

2/23/88 Amendment to IND, additional preclinical safety data

3/08/88 Amendment to IND, additional preclinical tox data (summary)

5/24/88 Amendment to IND, new protocol, Pharmacokinetics

6/09/88 Amendment to IND, annual report

8/05/88 Amendment to IND, submission of adverse experience, not related to drug

8/18/88 Amendment to IND, submission of preclinical safety data

8/29/88 Amendment to IND, additional preclinical safety data

9/02/88 Amendment to IND, submission of adverse experience report

10/04/88 Amendment to IND, preclinical safety report

10/26/88 Amendment to IND, final study report, percutaneous penetration

12/27/88 Amendment to IND, new investigators for protocols submitted 2/10/88

1/23/89 Amendment to IND, new investigators, T. cruris study, protocol submitted 2/10/88

3/06/89 Amendment to IND, new investigators, T. cruris study, protocol submitted 2/10/88

6/06/89 Minutes of FDA/Sandoz meeting, preclinical and clinical issues

6/21/89 Amendment to IND, annual report

7/18/89 Amendment to IND, preclinical safety data, monkey toxicology study and monkey pharmocokinetic study

8/28/89 Amendment to IND, preclinical safety data

9/07/89 Amendment to IND, final study reports of draft submitted 5/16/89

11/14/89 Amendment to IND, chronology of preclinical safety information, addresses issues from 6/6/89 meeting

7/06/90 Amendment to IND, new protocol & investigators SAN 2506-01, T. pedis (interdigital)

7/12/90 Amendment to IND, new protocol & investigators protocol SAN 2506-02

7/16/90 Amendment to IND, annual report

7/17/91 Amendment to IND, new protocol SAN 2508-01 terbinafine vs. clotrimazole in T. pedis

7/22/91 Amendment to IND, new investigators for SAN 2508-01

7/26/91 Amendment to IND, annual report

8/19/91 Amendment to IND, new investigators for SAN 2508-01

8/20/91 Amendment to IND, change in protocol SAN 2508-01, involves one site only

6/19/92 Amendment to IND, information amendment CMC information

6/29/92 Amendment to IND, new protocol SAN 2509-01, T. pedis, moccasin type

6/29/92 Amendment to IND, annual report

8/07/92 Amendment to IND, new investigators for SAN 2509-01 and 2509-02

12/22/92 Transfer of IND from Pharmaquest/Sandoz Vienna to Sandoz, E. Hanover

CHRONOLOGY OF REGULATORY ACTIVITIES

LAMISIL CREAM NDA 20,192

6/30/91	Original New Drug application submitted
7/08/91	Telephone request from FDA for desk copy of NDA volume No. 1 and 2
7/08/91	Submission of a copy of NDA volumes 1 and 2
8/14/91	Telephone request for copies of additional NDA volumes
8/16/91	Submission of copies of several NDA volumes
8/22/91	Telephone call to FDA for status update
9/18/91	Telephone request from FDA for information on pivotal clinical studies
9/30/91	Submission of information requested via telephone on 9/18/91
10/24/91	Telephone request and discussion regarding CMC information
10/28/91	Telephone request and discussion regarding CMC information
11/05/91	Submission of response to FDA telephone request of 10/28/91
11/15/91	Submission of a summary of the statistical analysis of efficacy data
12/02/91	Telephone request from FDA for an additional copy of an NDA volume
12/05/91	Submission of NDA volume requested by FDA on 12/2/91
12/19/91	Notification from FDA, our 11/15/91 submission is classified as a major amendment and 90 additional days are needed for the review, the new due date is 3/29/92
1/19/92	Telefax from FDA with CMC/microbiology questions
1/24/92	Telephone call to FDA to check status of review
1/29/92	FDA telephone request for SAS data diskettes
2/19/92	Submission of SAS data diskettes as requested on 1/29/92
3/18/92	Submission of results of clinical audits, withdrawal of

study 2-10, T. pedis moccasin type

2/28/92 Submission to respond to FDA telefax of 1/16/92

3/13/92 Notification from FDA, our 2/28/92 response to their 1/19/92 request is a major amendment requiring an additional 60 days, new due date 5/28/92

3/26/92 Submission of an updated foreign marketing status

5/18/92 FDA telephone request for statistical information

5/20/92 Submission of environmental assessment report

5/29/92 FDA notification regarding our 5/20/92 submission, major amendment requiring additional 60 days, new due date 7/20/92

6/05/92 Submission of supplemental analysis requested via telephone (FDA) on 5/18/92

6/10/92 FDA telephone request for additional statistical data (regrouping)

6/18/92 Submission of information (statistical regrouping) requested in FDA telephone conversation of 6/10/92

7/14/92 Notification from FDA that our submission of 6/18/92 is a major amendment and 60 additional days are needed, the new due date is September 18, 1992

8/17/92 Telephone request from FDA for clinical information

8/28/92 Submission of information requested on 8/17/92

9/24/92 FDA telephone request for information on clinical data

9/24/92 Submission of information requested this on this date

9/25/92 Submission of remaining information requested on 9/24/92

10/01/92 Receipt of 9/30/92 approvable letter for NDA 20,192

10/01/92 FDA telephone request for environmental protection certificate

10/07/92 Submission of environmental protection certificate requested on 10/1/92

11/03/92 Submission of response to approvable letter of 10/30/92

11/18/92 Submission of NON-US approved labeling as requested during a FDA meeting on 11/14/92

11/24/92	Submission of additional information in response to respond to approvable letter of 10/30/92
11/25/92	Telefax submission of Chile labeling for Lamisil
12/03/92	Submission of information telefaxed on 11/25/92
12/11/92	Telephone request from FDA for pooled data
12/14/92	Telephone request from FDA for a safety update
12/15/92	Submission of information requested via telephone on 12/11/92 and 12/14/92
12/17/92	Telefax from FDA with proposed labeling
12/23/92	Submission of proposal for alternate labeling
12/24/92	Telefax from FDA with proposed labeling
12/24/92	Teleconference with FDA to discuss labeling
12/28/92	Submission of proposal for changes to labeling
12/29/92	Telefax from FDA with proposed labeling
12/30/92	Teleconference with FDA to discuss labeling
12/30/92	Telefax of approval letter and labeling (dated 12/30/92) from FDA
1/04/93	Receipt of approval letter and labeling (dated 12/30/92) from FDA

APPENDIX E

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U. S. Patent No. 4,755,534

Issued: July 5. 1988

To: Anton Steutz

For: PROPENYLAMINES, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND THEIR USE AS PHARMACEUTICALS

Honorable Commissioner
of Patents and Trademarks
Washington, D.C. 20231

DECLARATION

Dear Sir:

Each of the undersigned representatives for Sandoz Ltd., which is the Applicant for Extension of Patent Term under 35 USC 156 respecting U.S. Patent 4,755,534 hereby declares as follows:

(1) That he is an official of Sandoz Ltd. authorized to obligate the corporation;

(2) That he has reviewed and understands the contents of the application being submitted herewith pursuant to 35 USC 156 and the Patent and Trademark Office's Rules on Patent Term Extension in 37 CFR '1.710 through '1.785;

(3) That he believes U.S. Patent 4,395,403 is subject to extension pursuant to '1.710 of said Rules on Patent Term Extension;

(4) That he believes an extension of the length claimed is fully justified under 35 USC 156 and the applicable regulations; and

(5) That he believes the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in '1.720 of said Rules on Patent Term Extension.

Each of the undersigned hereby declares further that all statements made herein of his own knowledge are true and that all

statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States code and that such willful false statements may jeopardize the validity of the application or any extension of patent term issuing thereon.

Further declarant sayeth not.

Signed this 23rd day of February, 1993.

P W Grubb L Vallet

Authorized Legal Representatives
For Sandoz Ltd.

Dr P. Grubb Dr L. Vallet